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Risk Factors of Otitis Media with Effusion in Children in a Portuguese population

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Dissertação de candidatura ao grau de Mestre em Medicina submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

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Assinaturas

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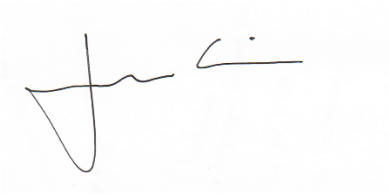

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Resumo

Introdução: A otite média com efusão é definida como a acumulação de fluído no ouvido médio, na ausência de sintomas ou sinais de infeção aguda ou inflamação. Em crianças, representa a causa mais comum de perda auditiva de condução leve a moderada. É considerada uma doença multifatorial, causada por fatores predisponentes dos quais alguns estão bem estabelecidos, enquanto outros permanecem controversos. A terapêutica desta condição é uma combinação entre vigilância, terapia médica e, em alguns casos, intervenção cirúrgica. A miringotomia pode ser realizada concomitantemente com colocação de tubos de ventilação e em combinação com adenoidectomia, quando indicada.

Objetivos: Determinar fatores clínicos e epidemiológicos relacionados com a repetição de miringotomia com colocação de tubos de ventilação

Métodos: Foi realizado um estudo retrospetivo com a aplicação de um questionário aos cuidadores das crianças submetidas a miringotomia com colocação de tubos de ventilação entre janeiro de 2014 e dezembro de 2016 no Centro Hospitalar do Porto. As crianças foram divididas em dois grupos (1: intervenção única/ 2: repetição da intervenção). As crianças portadoras de malformações craniofaciais assim como casos de *follow-up* incompleto foram excluídos. Compararam-se variáveis clínicas e epidemiológicas entre ambos os grupos. A idade, género, sazonalidade da cirurgia, excesso de peso/obesidade, grau de perda auditiva pré-operatória, intervenção cirúrgica nasal ou orofaríngea concomitante, número de irmãos, idade gestacional, tipo de amamentação, frequência de infantário, tabagismo passivo, estatuto socioeconómico, história de infeção das vias aéreas superiores ou otite aguda, roncopatia, atopia/alergia e refluxo gastroesofágico foram questionados.

Resultados: Trinta e uma crianças (14 do sexo masculino e 17 do sexo feminino com idade média 53.84 meses) submetidas uma única vez a miringotomia com inserção de tubos de timpanostomia e 35 crianças (23 do sexo masculino e 12 do sexo feminino com idade média 52.06 meses) com necessidade de repetição da intervenção foram comparadas. Os dois grupos não apresentavam diferenças estatisticamente significativas em idade ou género. O grau da perda auditiva pré-operatória ($p=0.008$) e sobrepeso ($p=0.014$) relacionavam-se com a necessidade de repetir a colocação de tubos de ventilação. A adenoidectomia concomitante, independentemente da idade, conferiu

menor necessidade de reintervenção (p=0.033). Não foram encontradas outras relações com significância.

Conclusão: Este é um dos primeiros estudos que compara miringotomia com colocação de tubos de ventilação única com a sua repetição. A recorrência da otite média com efusão parece ser superior nas crianças com maior grau de perda auditiva pré-operatória. Adenoidectomia concomitante pode reduzir o risco de intervenções sucessivas, independentemente da idade.

Palavras-chave: otite media; efusão; tubos de timpanostomia, risco, adenoidectomia

Abstract

Introduction: Otitis media with effusion is defined as the accumulation of fluid in the middle ear in the absence of signs or symptoms of acute infection or inflammation. In children it represents the most common cause of mild or moderate conductive hearing impairment. It is considered a multifactorial disease caused by predisposing factors, some well-established and some still controversial. Management of this condition is a combination of watchful waiting, medical therapy and, in some cases, surgical intervention. Myringotomy can be performed with or without tympanostomy tube placement and in combination with adenoidectomy, when indicated.

Objectives: To determine clinical and epidemiological factors related with repeated miringotomy with tympanostomy tube insertion.

Methods: Retrospective chart study and parental questionnaire of children submitted to myringotomy with tympanostomy tube insertion for chronic otitis media with effusion. The interventions performed between January 2014 and December 2016 in Centro Hospitalar do Porto were considered. The children were divided into two groups (1: *single myringotomy with tympanostomy tube insertion*/ 2: *repeated miryngotomy with tympanostomy tube insertion*). Children with craniofacial syndromes and incomplete or lost follow-ups were excluded. Clinical and epidemiological variables such as: age, gender, season when surgery was performed, hearing loss level before surgery, concomitant oropharyngeal or nasal surgical intervention, existence of siblings, gestational age, breastfeeding, nursery attendance, passive smoking exposure, parental socio-economic status, parent-reported history of ear infection, snoring, overweight/obesity, upper air-way infections, allergy and gastroesophageal reflux disease were compared between groups.

Results: Thirty one children (14 boys and 17 girls, with a mean age of 53.84 months) with single myringotomy with tympanostomy tube insertion and 35 children (23 boys and 12 girls, mean aged 52.06 months) with repeated myringotomy with tympanostomy tube insertion were compared. The two groups did not differ significantly in age or gender. A higher level of pre-op hearing loss ($p=0.008$) and overweight ($p=0.014$) were related with the need for repeated MTT. Adenoidectomy performed concomitantly, independently of age, conferred less need for re-intervention ($p=0.033$). No other significant relation was found between groups.

Conclusion: This is one of the first studies comparing single and additional tympanostomy tube placement. The level of pre-operative hearing loss is an indicative of chronic otitis media with effusion severity. Pediatric overweight maybe associated with reoccurrence of otitis media with effusion. Adjunctive adenoidectomy may decrease the risk of repeated surgery.

Keywords: otitis media; middle ear effusion; tympanostomy tubes; risk; adenoidectomy

Abbreviations

AOM – Acute otitis media
BMI – Body Masss Index
BMT – Bilateral myringotomy and tubes
IL – Interleukin
MEE – Middle-ear effusion
MTT – Myringotomy and tympanostomy tube insertion
OME – Otitis media with effusion
PAI-1 – Plasminogen activation factor inhibitor-1
TVT – Tympanostomy ventilation T-Tube
URI – Upper respiratory infection
WHO – World Health Organization

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Introduction

Otitis media with effusion (OME) is defined as the accumulation of fluid in the middle ear in the absence of signs or symptoms of acute infection or inflammation. If OME persists for over three months, it is considered chronic. [1, 2]

OME usually presents with asymptomatic middle ear serous or mucous accumulation of fluid (effusion) and may appear associated with a feeling of "plugged ear". [2, 3]

The real incidence and prevalence of OME is difficult to estimate due to lack of acute symptoms.[4] The estimated point prevalence varies between 7% and 13%. [5, 6] Globally, in the first year of life the incidence rate is highest.[7]

OME is the most common cause of mild or moderate conductive hearing impairment in children.[8] The impact ranges from no hearing loss up to moderate hearing loss (0 to 55 dB HL).[4] Typically children present mild hearing loss (about 25.28 dB HL) and 20% of the affected ears have levels exceeding 35 dB HL.[4] Other signs that may be attributed to OME include balance (vestibular) problems or ear discomfort.[3] It may also be related to difficulties in speech, reading, delayed response to auditory input and disturbances in attention[9] which can lead to poor school performance and behavior problems.[3]

The exact pathophysiology of OME is still uncertain, bacterial and viral infections as well as cellular and humoral immune responses are known to play a role.[10] It usually is concurrent with a viral upper respiratory tract infection.[11, 12] Yet, the main culprit seems to be dysfunction and impaired patency of the Eustachian tube.[4, 10] The child's Eustachian tube in comparison to the adult is shorter, more horizontal and floppy, which makes it less effective in ventilating and protecting the middle ear.[3] Thus, accumulation of effusion in the middle-ear may occur spontaneously due to deprived Eustachian tube function or as an inflammatory response following acute otitis media.[3]

OME has been associated with several risk factors. Several studies have shown an association between gastroesophageal reflux and OME.[6, 11] Similarly, there is a high prevalence of atopic conditions such as allergic rhinitis in children with OME.[6] Potentially modifiable risk factors include day care center attendance, lack of breastfeeding and exposure to tobacco smoke.[6, 12] Sex, race, premature delivery, number of siblings, socioeconomic status are also among the studied risk factors.[5, 6, 12]. Recently, evidence tends to associate OME with excessive weight.[13-15] All of these have been considered, however, some are still controversial.

OME in children with Down's syndrome or cleft palate is common.[16, 17] In this group, the prevalence ranges from 60% to 85% due to craniofacial bone abnormalities and immature development of the Eustachian tube.[16, 17]

Due to the possible correlation between OME and developmental problems in children, one of the most important parameters to take into account is their quality of life.[9]

Involvement of the tympanic membrane with retraction, perforation or atelectasis along with ossicular erosion or formation of cholesteatoma are possible consequences of OME, which do not occur often.[18]

The surveillance of children with chronic OME should include reevaluation at 3- to 6-month intervals.[3] Regular follow-up is important until fading of the effusion, significant hearing loss is identified or structural changes in middle-ear suspected – this allows early detection to prevent further complications.[3]

Management of OME is a combination of watchful waiting, medical therapy and in some cases, surgical intervention. It is recommended a minimum period of watchful waiting for 3 months prior to surgical intervention in the majority of cases [3] as OME is often self-limited when caused by an acute upper respiratory infection or when it postdates a recent ear infection as acute otitis media.[18, 19] The rate of spontaneous resolution, as shown by several reports, is approximately 20% in one month and 40% in three months. [19, 20] Myringotomy can be performed with or without tympanostomy tube (TVT) placement and in combination with adenoidectomy, when indicated. [3, 18]

Myringotomy with placement of a tympanostomy tube (MTT) is a means of removing middle-ear fluid, improving effusion-associated conductive hearing loss and maintaining an air-filled middle-ear space as long as the tubes remain patent.[21, 22]

Tympanostomy tubes remain in place for six to twelve months, depending on the type of tube (short-term versus long-term tubes).[23] Tubes tend to spontaneously extrude.[24]. Long-term tubes typically remain in place for more than 15 months, frequently requiring active removal.[25] The rate of repeated tympanostomy tube insertions varies from 19,9% [26] to 45%. [23]

The aim of this study is to determine clinical and epidemiological factors related to repeated myringotomy with tympanostomy tube insertion. Furthermore, it would aid to understand factors that may influence the persistence or reoccurrence of OME in order to optimize its treatment.

Materials and methods

Our sample contained children submitted to myringotomy with tympanostomy tube insertion because of chronic otitis media with effusion (OME), according to the AAO-HNSF 2013 Guidelines[3], between January 2014 and December 2016 in CICA-CHP (Centro Integrado de Cirurgia de Ambulatório do Centro Hospitalar do Porto). Additional criteria included children who were kept in follow-up care until extrusion of both tympanostomy tubes (in bilateral applications) with at least one reevaluation after. Children with craniofacial syndromes, incomplete or lost follow-ups were also excluded. Immediate follow-up care included analgesia and topic antibiotics. Protection against water is recommended as at home post-operative care.

In the repetition group, as to insure at least one year of follow-up, the second intervention could have been performed until December 2017. Children were divided into two groups (1: *single MTT* /2: *repeated MTT*). Instruments used comprised a retrospective chart study and the application of a parental questionnaire.

Clinical and epidemiological variables were compared between groups. Age, gender, pre-operative hearing loss level and surgical procedures information (such as concomitant oropharyngeal or nasal surgical intervention) were obtained from clinical records. Pre-operative hearing loss level was obtained from audiometry performed before the first intervention. All measurements are in decibel hearing level (dB HL), abbreviated to dB.

In order to collect epidemiologically relevant data on infants, a telephonic questionnaire was completed. The questionnaire regarded the child's status in the perioperative period. It included their height, weight, number of siblings, gestational age, breastfeeding, day-care centre attendance, exposure to passive smoking and parental reported history of ear infection, snoring, upper airway infections, allergy/atopy and gastroesophageal reflux disease as shown in Table I.

Height and weight were then categorized into the BMI according to the WHO: overweight is considered as a BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median and obesity is characterized as greater than 2 standard deviations above the WHO Growth Reference median. This data was clustered to a variable – overweight/obesity as Yes (classification as overweight or obesity) and No. Gestational age was categorized as preterm delivery under 37 weeks of gestation.

Socioeconomic status was graded using Graffar's Scale[27]. This scale is composed by five items (caregiver's employment, schooling, fonts of income, household conditions and area of residence) each with a score from 1 to 5. The sum of all scores (minimum 5, maximum 25) allows the classification of individuals into five categories: I – high; II – medium-high; III – medium; IV – medium-low; V – low.

The variables listed above were considered as potential risk factors influencing repetition of tympanostomy tube insertion.

The Ethics Committee of Centro Hospitalar do Porto approved this study.

All reported *P* values are two-tailed, with a *P* value < 0.05 indicating statistical significance. Analysis was performed with the use of SPSS version 20.0 (SPSS Inc, Chicago, USA).

Normal distribution was checked using Shapiro-Wilk test or skewness and kurtosis.

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions.

Comparison of the experimental groups were evaluated with the use of Student's T test or Mann-Whitney test, Chi-Square test or Exact Fisher test, as appropriate.

Results

Figure 1 shows the sample selection flowchart. From the 337 myringotomy with tympanostomy tube insertion performed within the time period, 35 children were re-interventioned. A random sample from the remaining cases (single myringotomy tube insertion) was selected (31 cases).

Table II summarizes demographic data comparing the *single MTT vs repeated MTT* group. 35 children underwent repeated MTT insertion representing 10.39% of the total 337 myringotomy with tympanostomy tube insertion. In this group, only one patient was submitted to unilateral insertion of tympanostomy tube in the first intervention. In the second surgery, three patients had unilateral insertions of the TVT (1 in the right ear; 2 in the left ear). The average time between interventions was 20.1 months. By the time of the second intervention the average age of the children was 72.17 months. The mean age at first procedure for patients undergoing a single MTT insertion was 53.84 months (range 27 to 129 months). The average age at the first MTT insertion for patients with subsequent procedure did not differ (52.06 months, range 26 to 76 months). The groups didn't differ significantly in age or gender. Gender was not a risk factor for subsequent MTT insertion (p=0.093). 23 male patients and 12 female patients constituted the *repeated MTT* group whereas 14 male patients and 17 female patients constituted the *single MTT* group. In total, male patients made 56.1% of the sample with female patients representing 43.9%.

Amigdalectomy was performed in approximately half of the patients. Turbinectomy was necessary in two patients of the *repeated MTT* group. Pre-operative hearing loss level

was obtained from audiometry performed before surgery, however, data from 15 patients was not available. The mean hearing threshold of the *repeated MTT* group was 34.9 dB whereas in *single MTT* group was 26.2 dB. A higher pre-operative hearing loss was associated with the need for re-intervention (p=0.008). This data is summarized in Table III.

A total of 57 patients (86.4%) had adenoidectomy performed at the time of their first MTT insertion. Independently of their age, as shown in Table IV, adenoidectomy performed concomitantly with MTT conferred less need for re-intervention (p=0.033).

As Table V shows, potential risk factors not associated with repeated MTT procedure include exposure to tobacco smoke, allergy/atopy, siblings, day-care attendance, snoring, gastroesophageal reflux, upper airway infections, breastfeeding, preterm delivery and repeated acute otitis media infections. Overweight (p=0.014) was related with the need for repeated MTT.

Regarding the Graffar scale, the total score did not differ between groups as demonstrated in Table VI.

Discussion

In our sample, statistically significant relationship between repeated MTT and pre-procedure higher hearing loss level was demonstrated. A higher level of pre-operative hearing loss may be related to the high incidence of repeated episodes of middle-ear effusion, thus meaning chronic OME.[4] In observational studies, bilateral OME has been associated with more severe hearing loss and decreased rates of spontaneous resolution (approximately 25 percent at six months and 30 percent at twelve months).[3, 24, 28] Although an association was found, no causal relationship can be stated.

An association with childhood overweight/obesity and repeated MTT was found in this series. Other studies have found a positive association between pediatric obesity and the occurrence of OME. [13-15] Obesity is considered a low-grade systemic inflammation state [29] with alterations in serum levels of different cytokine and other markers, IL-6 and C-reative protein are two examples.[30] IL-6, for example, is a proinflammatory cytokine that plays an important role in acute inflammatory responses[31], it has been detected in the middle-ear fluid of 84% of the patients with recurrent acute otitis media or chronic otitis media with effusion.[32] Furthermore, its concentration showed a significant correlation with IL-1β and TNF-α levels.[32]

IL-1β is a mediator of acute and ongoing inflammation of the middle ear, produced in early stages of inflammation able to intervein in the activation of neutrophils and lymphocytes.[32]

Results indicate that TNF-α can cause persistence or worsening of otitis media induced by bacterial infection.[30] The expression of TNF-α mRNA in middle-ear mucosa was found to be increased 8 to 16 weeks after OME induction via Eustachian tube obstruction.[31]

Increases in the concentrations of C-reative protein[29] and plasminogen activation factor inhibitor-1 (PAI-1)[33] have also been demonstrated in obese individuals. PAI-1 levels are high in mucoid effusions.[15] Interestingly, these factors either play a role in the pathogenesis of obesity or are associated with it. The similarity of cytokine profiles (e.g. tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, IL-8) in obese individuals and OME patients suggests a relationship between these conditions.[32]

Adipose tissue growing around the Eustachian tube and nasopharynx might predispose obese individuals to developing OME.[32]

As obesity persists after MT insertion, all these factors will continue to contribute to inflammation, thus perpetuating effusion and low rate of resolution of OME, after the extrusion of MT tubes.

Adenoidectomy performed concomitantly with MTT conferred less need for re-intervention, regardless of the age.

Adenoid hypertrophy has been reported in children with OME and is thought to play a role in OME development. [34, 35] The rationale behind adenoidectomy is the reduction of nasal obstruction, improved eustachian tube function and removal of a chronic nidus of infection from the nasopharynx. [34] Several trials have demonstrated its efficacy in reducing the morbidity of chronic OME in older children.[26, 36]

It has been stated that the benefit of adjuvant adenoidectomy is more beneficial in children with persistent OME aged ≥ 4 years.[37, 38]

In the CHP, exceptionally, adenoidectomy is performed independently of the child's age or symptoms, being that the obstructive forms of adenoids is the single criteria. Our finding does not go in agreement with the guidelines that advocate adenoidectomy to be performed after 4 years of age in symptomatic children.

One study showed that grade 4 adenoid hypertrophy was significantly more common in children with OME than in those without.[39] By the contrary, 40% of the children with OME presented with adenoid hypertrophy occluding more than 50% of the airway passage, which meant that 60% had lower grade adenoid hypertrophy.[35]

Instead, the degree of hypertrophy of laterally placed adenoids is thought to be more important in OME; unfortunately, this feature is not included in grading scales.[39-41]

The absolute size of the adenoids is not associated with OME, instead the presence of laterally placed adenoid tissue around the *torus tubarius* is.[42]

Additionally, chronic adenoid infection may act as a source of pathogens which can spread to the middle ear via Eustachian tube.[43]

Adenoidectomy performed simultaneously to MTT may prevent MTT repetition.[26, 38] This may support the need to integrate the position of the adenoids in the criteria for adenoidectomy in the OME cases, regardless of age or nose symptoms.

No association between Graffar scale results and MTT repetition was found in our study. Interestingly, according to the mean value, the overall social classification of each group would be different. The *repeated MTT* group would be considered Class II as the s*ingle MTT* group would be classified Class III. In current literature, low mother education and poor educational status of the parents are risk factors for OME [5, 6]. In one study, higher parental education level seemed to be related with persistence or reoccurrence of OME.[44]

It has been shown that male patients are more likely to undergo MTT procedures than female patients.[26] In our sample, male patients outnumbered female patients. However, gender was not a risk factor for additional MTT procedure.

Allergic conditions, such as allergic rhinitis, cause nasal inflammation with impaired eustachian tube function.[42] It is also associated with inferior turbinates hypertrophy and more frequent and persistent nasal infections with retrograde OME via the Eustachian tubes.[42] An association between atopy/allergy and repetition of MTT insertion was not found in our study. As OME is acknowledged, concomitant allergic conditions are usually also discovered and managed. Their treatment may resolve or, at least, attenuate the allergy mechanism that influences OME.

This retrospective review has potential limitations. First, the small sample size may interfere with the results - a bigger sample would give strength to the conclusions. A reporting bias could have affected our incidence of risk factors. They may not have been accurately communicated in all cases. In addition, recall biases could affect our record of repeated upper airway respiratory infections or recurrent acute otitis media as it relies on parents' or caregivers' answers. Confounding factors could contribute to the need of repeated surgery such as the parental engagement in postoperative care, time period for TVT extrusion and postoperative complications.

Further research is needed to explore prognostic factors for OME which may be important for early intervention and strategy definition.

Conclusion

In conclusion, OME during infancy is a common and multifactorial disease. In agreement with previous studies, we found that adenoidectomy, performed at the time of initial or subsequent myringotomy with ventilation tube insertion, reduced the need for additional intervention. Supplementary research is needed to determine which subgroups of children will benefit most from adenoidectomy at the time of the initial tube placement.

An association with childhood obesity and repeated MTT was found in this series.

Albeit of our outcomes, other intrinsic or extrinsic factors may still play a more or less important role in the reoccurrence of OME. Further study is needed for better understanding of the underlying processes.

Figures

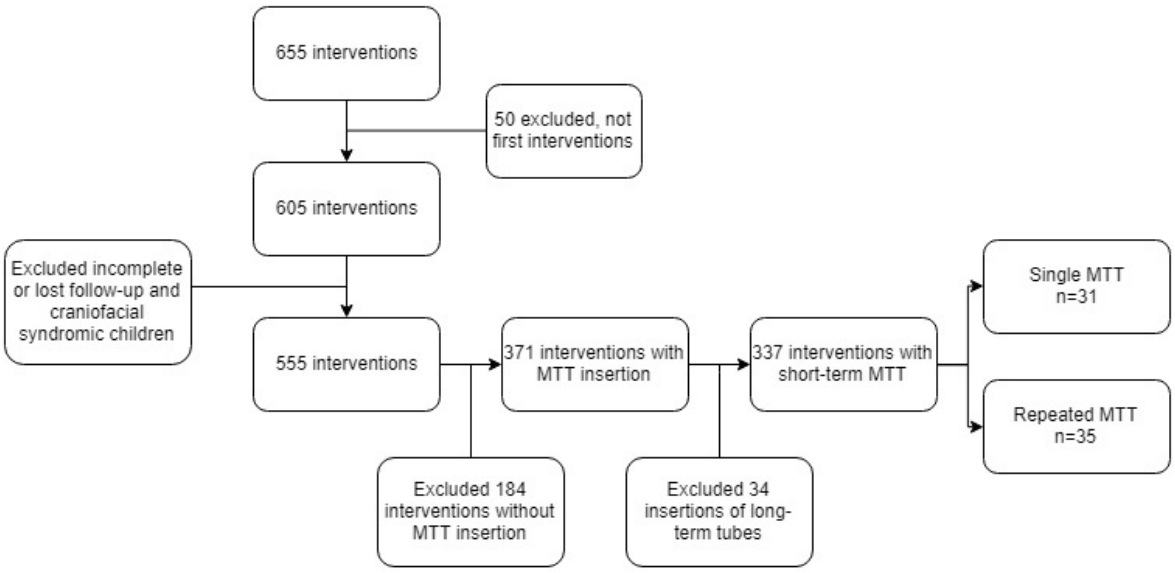

FIGURE 1. SAMPLE FLOWCHART

Tables

TABLE I - TELEPHONIC QUESTIONNAIRE

1. Number of siblings
2. Passive smoking
3. Gestational age at birth
4. Height and weight
5. Day-care center attendance
6. Infant nutrition during the first 6 months
7. How frequently did your child suffer a common cold?
8. Did your child snored during his sleep?
9. Atopic/allergic conditions
10. Gastroesophageal reflux disease
11. How frequently did your child suffer from ear infection?

TABLE II – CHARACTERISTICS OF BOTH GROUPS

Variable		Group		Total (%)
		Repeated MTT (n=35)	Single MTT (n=31)	
Gender, n. of children	Male	23	14	37 (56.1%)
	Female	12	17	29 (43.9%)
Age 1st intervention, in months	Mean (±SD)	52.06 (±14.01)	53.84 (±20.44)	_
Age 2nd intervention, in months	Mean (±SD)	72.17 (±16.59)	_	_
1st surgery laterally, n. of children	Right	1	2	3 (4.5%)
	Left	0	2	2 (3.0%)
	Bilateral	34	27	61 (92.4%)
2nd surgery laterally, n. of children	Right	1	_	_
	Left	2	_	_
	Bilateral	32	_	_
Time between surgeries in months	Mean (±SD)	20.1 (±7.79)	_	_
	Range	6.7 to 40.9		

TABLE III - RISK FACTORS RELATED TO THE INTERVENTIONS

Variable		Group		p-value
		Repeated MTT	Single MTT	
Season, n. (%)	April-Sep	17 (48.6%)	13 (41.9%)	
	Oct-March	18 (51.4%)	18 (58,1%)	
				0,268
Adenoidectomy n. (%)		26 (74.3%)	31 (100%)	0,002
Amigdalectomy n. (%)		16 (45.8%)	17 (59.9%)	0,622
Turbinectomy n. (%)		2 (5.7%)	0	0,494
Pre-op hearing loss (dB), mean (±SD)		34.9 (± 9.0)	26.2 (±11.0)	0,008

TABLE IV – ADENOIDECTOMY IN CHILDREN UNDER FOUR YEARS OLD

	Group		p-value
	Repeated MTT	Single MTT	
Adenoidectomy (under 4 years old) n. (%)	8 (22.9%)	14 (45.2%)	0,033

TABLE V – RISK FACTORS RELATED TO THE CHILD

	Group		
	Repeated MTT	**Single MTT**	**p-value**
Gender, n. of males (%)	23 (45.7%)	14 (45.2%)	0,136
Siblings, n. of children with sibilings (%)	24 (68.6%)	19 (61.0%)	0,609
Parental Smoking, n. of children exposed (%)	21 (60.0%)	19 (61.0%)	1
Overweight, n. of obese + overweight children (%)	11 (31.4%)	2 (6.4%)	0,014
Day-care attendance, n. of children entering < 48 months old (%)	21 (60.0%)	20 (64.5%)	0,801
URI's, n. of children with ≥2 URI's per month (%)	15 (42.9%)	8 (25.8%)	0,355
Snoring, n. of children (%)	31 (88.6%)	23 (74.2%)	0,201
Repeated AOM, n. of children (%)	31 (88.6%)	21 (67.7%)	0,068
GERD, n. of children (%)	7 (20%)	2 (6.5%)	0,156
Atopy/Allergy, n. of children (%)	20 (57.1%)	14 (45.2%)	0,460
Breastfeeding, n. of children feeded with formula < 6 months old (%)	6 (17.1%)	10 (32.2%)	0,109
Preterm delivery, n. of children (%)	9 (25.7%)	7 (22.6%)	0,783

Abbreviations: Upper respiratory infections (URI's), Acute otitis media (AOM), Gastroesophageal reflux disease (GERD).

TABLE VI – GRAFFAR SCALE

	Group		
	Repeated MTT	**Single MTT**	**p-value**
Graffar Index, Mean (± SD)	13(± 4)	15 (±3)	0,063

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